Ocular tuberculosis

Ocular tuberculosis: More than 'Of Mice and Men'

Journal:	*Ocular Immunology and Inflammation*
Manuscript ID	NOII-2020-0428.R1
Manuscript Type:	Letter to the Editor
Date Submitted by the Author:	08-Jul-2020
Complete List of Authors:	Mitchell, Jordan; The Royal (Dick) School of Veterinary Studies and The Roslin Institute, Division of Veterinary Clinical Sciences Ganis, Laura; Barts Health NHS Trust, Blacklock, Benjamin; The Royal (Dick) School of Veterinary Studies and The Roslin Institute, Division of Veterinary Clinical Sciences Petrushkin, Harry ; Moorfields Eye Hospital NHS Foundation Trust, Uveitis and Scleritis service Hope, Jayne; The Royal (Dick) School of Veterinary Studies and The Roslin Institute Gunn-Moore, Danielle; The Royal (Dick) School of Veterinary Studies and The Roslin Institute
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Authors:

Jordan L Mitchell[1], BVM&S MRCVS

Laura Ganis[2], BSc MBBS

Benjamin T Blacklock[1], BVSc (Hons) DiplECVO MRCVS

Harry Petrushkin[3,4], PhD FRCOphth

Jayne C Hope[1], BSc PhD FRSB

Danièlle A Gunn-Moore[1], BSc (Hons) BVM&S PhD MANZCVS FHEA FRSB FRCVS RCVS Specialist in Feline Medicine

Affiliations:

1. Royal (Dick) School of Veterinary Studies and The Roslin Institute, The University of Edinburgh, Easter Bush, Midlothian, EH25 9RG, UK

2. The Royal London Hospital, Barts Health NHS Trust, Whitechapel Road, Whitechapel, London, E1 1FR, UK

3. Uveitis and Scleritis Service, Moorfields Eye Hospital Foundation Trust, 162 City Road, London, EC1V 2PD, UK

4. Rheumatology Department, Great Ormond Street Hospital, Great Ormand Street, London, WC1N 3JH, UK

ORCID iD:

Jordan L Mitchell: 0000-0001-6755-3214

Laura Ganis: 0000-0003-4269-3581

Harry Petrushkin: 0000-0002-4662-2994

Jayne C Hope: 0000-0001-6573-6172

Danièlle A Gunn-Moore: 0000-0003-2088-503X

Corresponding Author Address Details:

Jordan L Mitchell

Email: jordan.mitchell@ed.ac.uk

Postal address (work): The Roslin Institute, The University of Edinburgh, Easter Bush, Midlothian, EH25 9RG

Funding Details: Jordan Mitchell is supported by a Biotechnology and Biological Sciences Research Council (BBSRC) studentship (BB/M010996/1). Jayne Hope is funded by BBSRC Institute Strategic Programme funding (BB/P013740/1 & BBS/E/D/20002174).

Word Count: 1651 (excluding abstract, keywords and references)

Abstract

Tuberculosis (TB), caused by infection with members of the *Mycobacterium tuberculosis*-complex, is one of the oldest known infectious disease entities, resulting in the death of millions of humans each year. It also results in a substantial degree of morbidity and mortality in animal species. Extrapulmonary TB is well-recognised in humans, and the eye is one site that can be affected. Studies seeking to understand ocular TB have often relied on animal models; however, these have their limitations and may not truly reflect what happens in humans. We wish to raise awareness among ophthalmologists and vision scientists of naturally occurring cases of ocular TB in animals, namely cattle and domestic cats, and the possibilities of gaining further understanding of this presentation of TB by adopting a collaborative approach. This will hopefully improve outcomes for both human and animal patients.

Keywords: ocular, tuberculosis, zoonosis, uveitis, feline, bovine

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Tuberculosis (TB), predominantly caused by *Mycobacterium* (*M.*) *tuberculosis*, remains the largest single infectious cause of death in humans, with 10 million individuals becoming ill with TB in 2018 and a reported 1.5 million TB-related deaths.[1] Although predominantly an infection of the lungs, extrapulmonary TB accounted for 15% of the 7 million incident cases of TB recorded in 2018;[1] one site that can become affected is the eye. Ocular TB (OTB) is thought to originate from haematogenous dissemination of bacteria from a site of primary infection *i.e.* the lungs to the eye,[2] and while every ocular tissue can become affected,[3] choroidal tubercles are the most common presentation of disease.[4]

There has been renewed interest in animal models of OTB, and the advantages and limitations of these have recently been reviewed.[5] Animal models allow us to ask questions that would not be possible in human studies; however, these host-pathogen interactions could be deemed artificial, they may not truly reflect the progression of disease in humans, and the ethics of using experimental research animals should be considered. Progress has been made in the use of *in vitro* models, although further development is required to allow complete exploration of such a complex structure.[6] Following the review by Basu *et al*.,[5] we propose that naturally occurring cases of OTB in animals may provide more meaningful results than current animal models, and through this communication we seek to raise awareness of these infections; human and veterinary medicine benefit when they work alongside one another, and a shared understanding and interest in this field could greatly assist all patients, whether they ambulate on two limbs or four.

While TB refers to infection with members of the *M. tuberculosis*-complex,[7, 8] non-tuberculous mycobacteria can also cause ocular disease in humans[9, 10] and animals.[11-15] Reports of OTB in animals are often limited to small case studies, resulting in gaps in our knowledge of the dynamics of these infections, as well as species-to-species variation. Of the species susceptible to developing TB, cattle are the obvious animal to investigate further, given the high prevalence of bovine TB (bTB) in parts of the world such as the United Kingdom and the Republic of Ireland.[16] The most common cause of bTB is *M. bovis*, which can also cause disease in humans;[1] resultantly, the term "zoonotic TB" has been used for *M. bovis* infections in humans.[17] One of the benefits of using cattle to study OTB is the highly homologous immunopathology between bTB and human TB.[18, 19] While reports of OTB in cattle are rare,[20-22] preliminary studies by the authors have shown ocular signs present in a number of eyes taken

from animals infected with *M. bovis* (Figure 1) (unpublished data). Clinically, ocular bTB presents similarly to disease in humans, with silent choroidal granulomas which can result in a subretinal exudate and retinal detachment.[20, 21] Disease is thought to originate from haematogenous dissemination of bacteria from the lungs, mirroring the proposed route of human ocular infection. Anterior uveitis and keratitis have also been reported.[20, 22] Further work is required to establish the prevalence of ocular bTB, as well as provide more detailed descriptions of the macrophenotypic presentations of disease, but cattle may prove a useful animal model in the future.

An often-overlooked species to investigate further would be the domestic cat. Once considered a historical disease associated with the consumption of raw milk from tuberculous cows, feline TB has been increasingly recognised in Great Britain in recent years,[23, 24] and is of importance because of the potential zoonotic risk.[25] Feline TB is caused by infection with either *M. bovis* or the vole bacillus, *M. microti*;[23] of note, cats appear highly resistant to infection with *M. tuberculosis.*[26] Feline TB typically presents as a nodular cutaneous disease; pulmonic involvement is putatively due to haematogenous spread of bacteria from the site of primary infection.[27] Genetically *M. microti* is very similar to *M. bovis*-BCG,[28] and historically it was used in TB vaccinations for humans as it had been assumed to be avirulent,[29] as it lacks key virulence factors encoded on the region of difference 1 (RD-1) locus of the genome.[30, 31] These RD-1 factors have traditionally been thought of as key for mycobacterial virulence, yet the extent of disease due to *M. microti* in the domestic cat,[32-34] and other species such as dogs,[35] goats,[36] meerkats,[37] alpaca and badgers,[29] shows this pathogen can have devastating consequences. Additionally, a small number of cases of *M. microti* TB have also been recorded in humans.[38]

In Great Britain, just over 6% of cats with mycobacterial disease present with ocular signs,[23] which can result from infection with both tuberculous and non-tuberculous mycobacteria.[39-44] Unlike in humans and cattle, cases of feline OTB typically present as clinically fulminant disease with active lesions,[39, 44] and the consequences of untreated disease can be devastating. Feline OTB has been recognised since the early 20th century, with reports featuring in prominent medical ophthalmology journals,[45] and there has been recent renewed interest in this disease entity.[44] Most cases of OTB appear to result from *M. bovis* infection, though *M. microti*-associated disease has also been identified.[44] Cases often present with signs attributable to uveitis, which can vary from localised findings including scleral injection, corneal oedema, aqueous flare and a swollen iris to subtle changes associated with pain, namely hyporexia and lethargy;[44] these changes may be subtle and not readily appreciated. Fundoscopic

examination typically identifies solitary choroidal tubercles or tuberculomas (Figure 2).[44] Retinal detachment often accompanies choroidal lesions, with an associated subretinal exudate and haemorrhage; these cats will typically present with fixed, dilated pupils and are non-visual.[39, 44, 45] Secondary complications of uncontrolled uveitis, such as cataract formation and glaucoma, have also been recorded.[39, 44] Other phenotypes seen in humans, such as serpiginous-like choroiditis and retinal vasculitis have not been documented in cats with OTB; although retinal vasculitis is a classical finding in cats with ocular manifestations of feline infectious peritonitis.[46] Corneal and conjunctival granulomas have been recorded in cats,[44] but lesions affecting tissues other than the uvea or retina are less common. Histologically, granulomatous to pyogranulomatous inflammation is the dominant finding in feline OTB lesions,[44] however multinucleated giant cells, a hallmark of tuberculous lesions in other species, including those affecting ocular tissues,[47] are rare in cats.[44, 48] Cases of feline OTB may present with or without systemic disease.[39, 44, 49]

Of the other species susceptible to TB, naturally occurring disease is only frequently identified in South American camelids (SAC),[50] lions[51] and badgers;[52, 53] while reports of OTB in SAC are lacking, the authors are aware of possible cases in the United Kingdom and investigations into these are ongoing (Dr S. J. Moore, personal communication, 18 June 2020). The pathology of OTB in lions appears similar to domestic cats, with reports of *M. bovis* causing granulomatous uveitis and subsequent retinal detachment.[54] As for SAC, OTB has not been reported in badgers. Cases of canine TB are uncommon, and dogs appear to be more resistant to mycobacterial infections compared to cats, but they are susceptible to *M. tuberculosis*,[55] posing a risk to human health.[56] Ocular involvement in canine TB is rare, with lesions most often present within the choroid.[57] Psittacines can also develop disease due to *M. tuberculosis* infection, where it can result in retro-orbital infection[58] or tubercles on the nictitating membrane as part of a disseminated disease process.[59] Disseminated disease resulting in OTB has also been observed in pigs[21] and non-human primates;[60] sometimes ocular signs may be the only observed clinical finding. Determining the extent of disease is essential for the appropriate treatment of both human and animal cases.[2, 44, 61]

The exact pathogenesis of ocular involvement in TB in animal species is unknown; it could mirror human infection, with haematogenous seeding of bacteria from a primary site of infection to the eye, it may result from direct ocular injury or it could be a sterile inflammatory response to infection elsewhere in the body. Our ongoing studies are exploring the histopathology and immunology of feline TB lesions to

expand our knowledge of host-pathogen interactions, the extent to which ocular structures are affected (Figure 3), and whether infectious agents are present within the eye. Antigenic mimicry between *M. bovis*-BCG and retinal antigens may be the cause of uveitis, chorioretinitis, other retinopathies and optic neuropathy in some humans;[62-66] it is unknown whether this phenomenon occurs in other species. The difference between knowing whether the eye contains infectious organisms, or if the clinical signs signify local hypersensitivity, could influence the management of OTB across all species.[65, 66] While most cases of human OTB are presumptive, diagnosed with the eye *in situ* and treated with systemic anti-mycobacterial therapy,[2, 61] the diagnosis of feline OTB is often achieved on histopathology of the enucleated globe. Anti-mycobacterial treatment is then given to target any residual, or systemic infection. If such cases can be successfully identified and treated without requiring enucleation, as achieved with humans, this may provide a more positive outcome for cats and their owners. For human ophthalmologists, these findings could identify more appropriate, spontaneous models to study the pathology of OTB. They could also facilitate diagnosing these infections,[67] as well as inform whether prolonged courses of systemic anti-mycobacterial therapy are necessary for successfully treating OTB or whether treating the inflammatory component of the disease is sufficient if the pathology is not driven by active infection.[65, 66]

Ocular TB should not be thought of as solely a human disease; while not identical, this condition is also recognised in many species including cattle and cats. The underlying immunopathology of TB is similar between humans and cattle, and this species may provide more beneficial insights to OTB than the laboratory animal species currently used. While the feline immune response to mycobacterial infection differs from that of humans,[48] comparative studies can be undertaken to ask what similarities and differences are observed, why this happens and subsequently what can be done to improve outcomes for both species. The best way to combat these zoonotic infections is not to divide knowledge between the species, but to share our collective understanding for the benefit of all.

Acknowledgements: We would like to thank Dr Emma Scurrell for providing tissue samples and histopathological interpretation, Dr Jo Moore and Professor Sheila Crispin for their clinical input and advice and the veterinary staff, owners and pets who have contributed to ongoing research into mycobacterial disease at The University of Edinburgh.

Disclosure of Interest: The authors report no conflict of interest.

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Figure Captions

Figure 1: Fundoscopic examination of the eye from a cow with confirmed *Mycobacterium bovis* infection showing a choroidal granuloma (black arrow).

Figure 2: Fundoscopic examination of the eye of a cat with suspected tuberculosis, showing a choroidal granuloma (black arrow) within the region of the non-tapetal fundus. (Image courtesy of David Gould MRCVS).

Figure 3: Haematoxylin and eosin stained section of the globe from a cat diagnosed with *Mycobacterium bovis* by interferon-gamma release assay testing[68]. There is evidence of granulomatous to pyogranulomatous chorioretinitis (black arrow) extending into the anterior uvea (red arrow); there is also blockage of the drainage angle (white arrow). The retina is detached (blue arrow) and there is posterior rupture of the lens capsule (purple arrow), with subsequent neutrophilic phakitis. Scale bar = 1mm. Magnification x18.

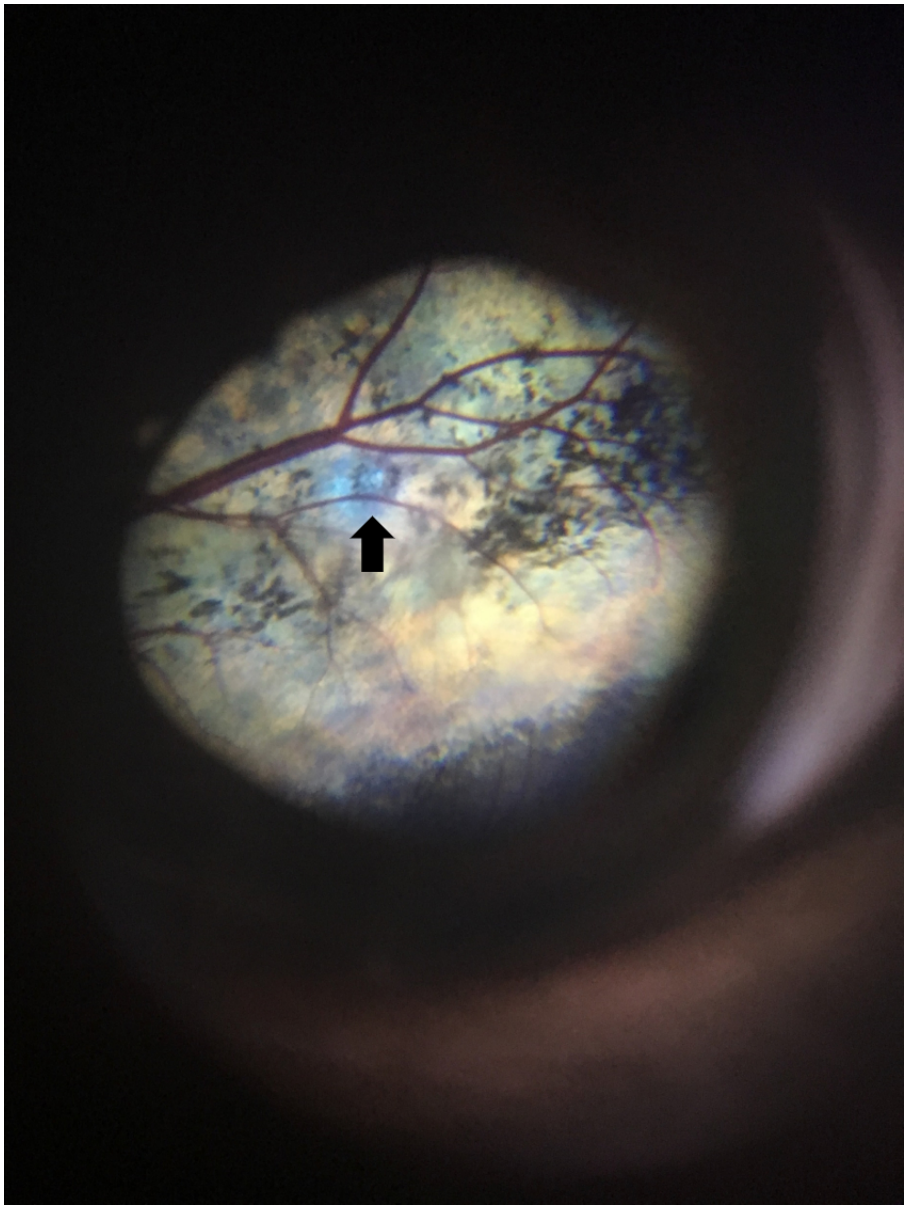

Figure 1: Fundoscopic examination of the eye from a cow with confirmed *Mycobacterium bovis* infection showing a choroidal granuloma (black arrow).

71x95mm (300 x 300 DPI)

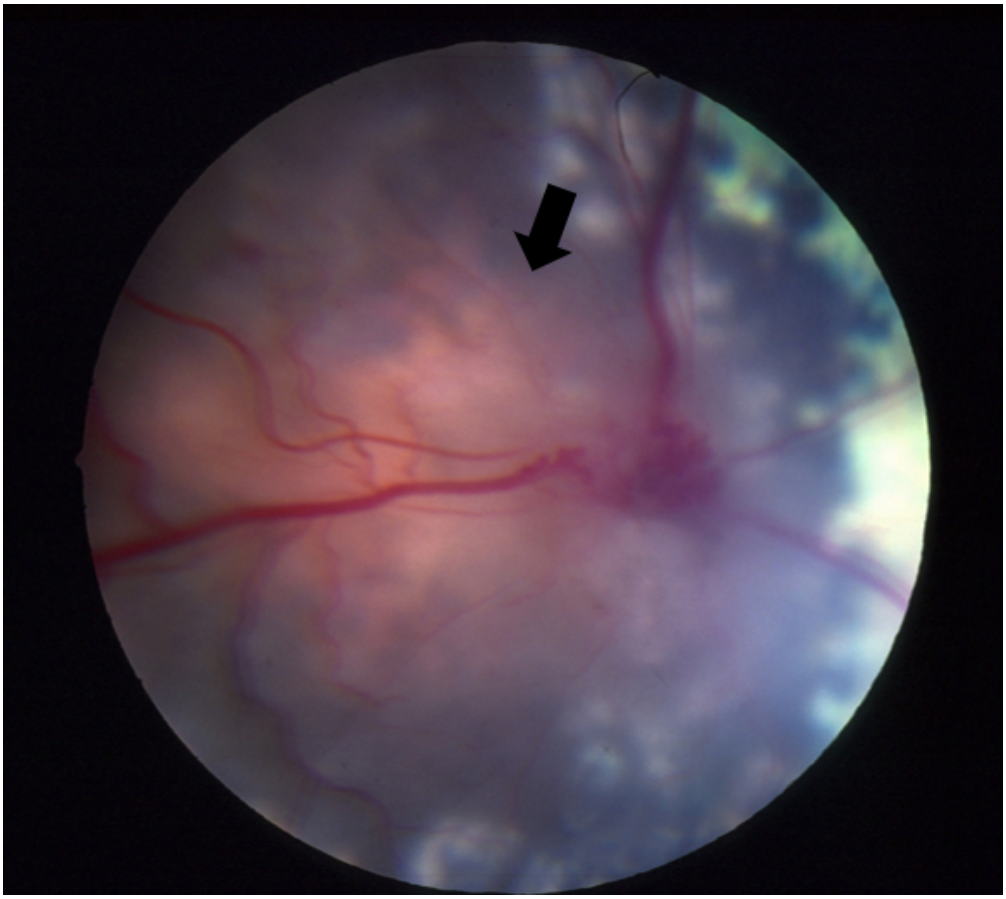

Figure 2: Fundoscopic examination of the eye of a cat with suspected tuberculosis, showing a choroidal granuloma (black arrow) within the region of the non-tapetal fundus. (Image courtesy of David Gould MRCVS).

49x43mm (300 x 300 DPI)

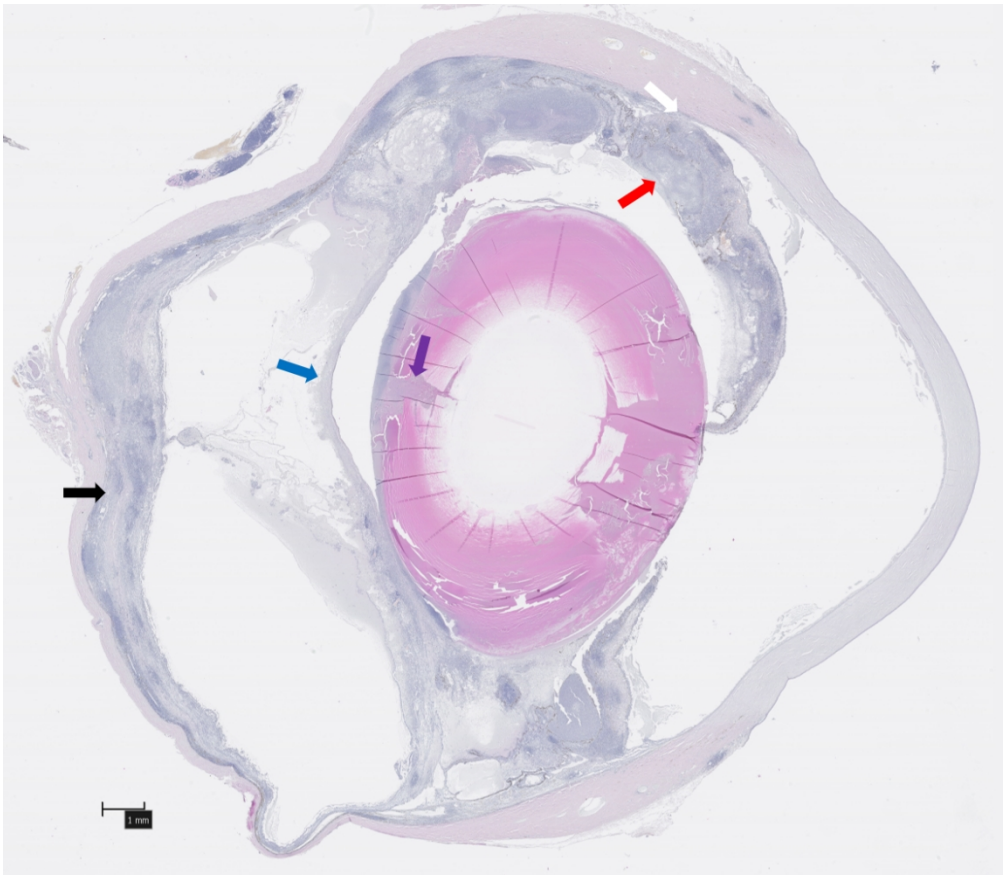

Figure 3: Haematoxylin and eosin stained section of the globe from a cat diagnosed with *Mycobacterium bovis* by interferon-gamma release assay testing[68]. There is evidence of granulomatous to pyogranulomatous chorioretinitis (black arrow) extending into the anterior uvea (red arrow); there is also blockage of the drainage angle (white arrow). The retina is detached (blue arrow) and there is posterior rupture of the lens capsule (purple arrow), with subsequent neutrophilic phakitis. Scale bar = 1mm. Magnification x18.

99x86mm (300 x 300 DPI)